A Review of the Clinical, Economic, and Societal Burden of Treatment-Resistant Depression: 1996–2013

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Objective: **This literature review assessed the burden of treatment-resistant depression in the United States by compiling published data about the clinical, societal, and economic outcomes associated with failure to respond to one or more adequate trials of drug therapy.** ***Methods:*** **PubMed and the Tufts Cost-Effectiveness Analyses Registry were searched for English-language articles published between January 1996 and August 2013 that collected primary data about treatment-resistant depression. Two researchers independently assessed study quality and extracted data.** ***Results:*** **Sixty-two articles were included (N=59,462 patients). Patients with treatment-resistant depression had 3.8±2.1 prior depressive episodes and illness duration of 4.4±3.3 years and had completed 4.7±2.7 unsuccessful drug trials involving 2.1±.3 drug classes. Response rates for treatment-resistant depression were 36%±1%. A total of 17%±6% of patients had prior suicide attempts (1.1±.2 attempts per patient). Quality-of-life scores (scale of 0–1, with 0 indicating death and 1 indicating perfect health) for patients with treatment-resistant depression were .41±.8 and .26±.8 points lower, respectively, than for patients who experienced remission or response. Annual costs for health care and lost productivity were $5,481 and $4,048 higher, respectively, for patients with treatment-resistant versus treatment-responsive depression.** ***Conclusions:*** **Treatment-resistant depression exacts a substantial toll on patients' quality of life. At current rates of 12%–20% among all depressed patients, treatment-resistant depression may present an annual added societal cost of $29–$48 billion, pushing up the total societal costs of major depression by as much as $106–$118 billion. These findings underscore the need for research on the mechanisms of depression, new therapeutic targets, existing and new treatment combinations, and tests to improve the efficacy of and adherence to treatments for treatment-resistant depression. (*Psychiatric Services* 65:977–987, 2014; doi: 10.1176/appi.ps.201300059)**

Almost 50% of the U.S. population has experienced at least one psychiatric disorder in their lifetime (1). The lifetime prevalence of major depressive disorder is reported to be as high as 17%, and the 12-month prevalence is 5%–9% (2–4). The World Health Organization ranks major depressive disorder among the diseases that are most debilitating to society, in part because of its association with increased utilization of health care resources, diminished quality of life, and indirect personal and societal costs (5,6).

More than 50% of patients with major depressive disorder do not reach remission with an initial treatment; of those, 30%–50% also do not respond (4,5,7–9). The designation "treatment resistant" is used to describe patients who do not respond to antidepressant therapy after one or more adequate trials (9–11) (duration of at least six weeks and use of appropriate dosages [12–15]). A response to treatment is commonly measured as a ≥50% decrease in baseline scores on the Hamilton Rating Scale for Depression (HAM-D) (7). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial studied the effectiveness of different treatments for major depressive disorder among patients who did not become symptom free after one or more treatments. Seventy-two percent of patients did not experience remission after treatment with citalopram, the initial medication used in this study; with each subsequent treatment, failure to remit increased from 79% to 84% to 93% (8,16–19).

Patients with treatment-resistant depression contribute a disproportionately high burden of illness compared with patients who respond to treatment. Several studies have documented

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a subset of outcomes related to treatment-resistant depression, such as societal costs and effects on quality of life, labor force participation, or medical resource utilization, but none has provided a comprehensive, systematic, and rigorous review of the overall burden.

The aim of this systematic review was to assess the aggregate burden of treatment-resistant depression in the United States by compiling the data available from published studies on clinical, societal, and economic outcomes associated with treatment-resistant depression. The review assessed characteristics and comorbid conditions, costs of treatment, mortality, quality of life, severity of symptoms, response rates to subsequent treatments, and adverse events among patients with treatment-resistant depression. This review also investigated factors that contribute most to the societal burden of treatment-resistant depression and identified potential areas for improvement.

Methods

We used PubMed to search MEDLINE for articles published between January 1996 and May 2011 by using terms related to treatment-resistant depression, outcomes, economics, and society. A supplemental search of PubMed using additional terms was conducted for articles published between May 2011 and August 2013. We also conducted a search of the Tufts Cost-Effectiveness Analysis Registry (20) for articles published from 1996 through 2013 and reviewed the reference lists of articles identified by the searches related to costs of treatment. [A complete list of search terms and a full description of the study methods are available online as a data supplement to this article.]

Two researchers screened each abstract of the retrieved articles. The articles were included if the abstract referred to primary data collection as a part of the design; if endpoints of the study were pertinent to clinical, societal, or economic outcomes; and if the study enrolled adults ages 18 and older. We defined treatment resistance as failure to respond to one or more adequate trials of drug therapy. This definition was intended to conform to accepted criteria of treatment resistance while including heterogeneous definitions. The evidence grade for each study was assessed by using the quality index developed by the Mental Disorders and Illicit Drug Use Expert Group (21). Quality index scores range from 0 to 17, with higher scores indicating that more complete reporting and higher quality methods were used.

We included articles that reported results from the STAR*D trial, even though its definition of treatment resistance as "failure to remit" is more inclusive than the one used in this review, which included patients who failed to respond. However, as the largest and longest study evaluating depression treatment, the STAR*D study provides valuable information for comparing responses to treatment, despite differences in definitions of treatment resistance.

Summary statistics were performed by using Stata, version 9.2, and were weighted by sample size. Unless stated otherwise, results are reported for the treatment-resistant population.

Results

Literature search and study characteristics

The original search identified 442 articles; 62 were included in this review. [The complete list of included articles is available in the online data supplement.] The mean±SD study duration was 7.75±1.75 years. The quality index score varied from 6 to 18 (mean±SD=13±3). Sample sizes in the studies varied from six to 24,415 patients (median=42; Table 1) and, together, enrolled 59,462 patients. Thirteen studies summarized data on outpatients, eight on inpatients, and six on both populations; 22 articles did not specify a population but likely included predominantly outpatients.

Baseline patient characteristics

Patients' baseline characteristics varied by study (Table 1). The mean age was 46.7, and illness duration was 4.4 years. Women represented 71% and non-Hispanic whites represented 89% of the study populations. Patients had 3.8 prior depressive episodes (range .8–7.2). On average, patients had not responded to 4.7 drug trials (range 1–10) and 2.1 drug classes (Table 2).

Symptom severity

The scales used to assess symptom severity varied greatly. Commonly used scales included the HAM-D, the Montgomery-Asberg Depression Scale (MADRS), the Clinical Global Impression–Severity (CGI-S) scale, and the Quick Inventory of Depressive Symptomatology–Clinician Rated (QIDS-C). The average scores at baseline on the HAM-D-17, the MADRS, the CGI-S, and the QIDS-C indicated that symptom severity was within or close to the scoring range used to classify conditions as severe or markedly ill (Table 2) (22–32). At the end of the studies, severity scores had improved by an average of 35%±8% (improvements of 12.8±4.1, or 42%, on the HAM-D-17; 23.2±7.7, or 27%, on the MADRS; and 3.0±1.4, or 36%, on the CGI-S). Scores at the end of the studies were not reported for the QIDS-C.

Comorbid conditions

Comorbid conditions were relatively common among patients with treatment-resistant depression, as indicated in Table 1. Comorbid conditions included joint, limb, or back pain (73%); hypertension (67%); and dyslipidemia (61%) (33,34). Some psychiatric conditions, such as malaise or fatigue, anxiety, and personality disorder, were more prevalent among patients with treatment-resistant versus treatment-responsive depression (15,33–37). Suicidal ideation was reported for 15%±8% of patients with treatment-resistant depression, 6% of patients with treatment-responsive depression, and 1% of the general population (33,38,39). Approximately 17%±6% of patients with treatment-resistant depression had a history of suicide attempt, with an average of 1.1±.2 prior suicide attempts each (8,15,33,39–44).

Mortality rates (deaths per 1,000 patient-years) were similar among patients with treatment-resistant (46.2) and treatment-responsive (46.8) depression in a Medicare population and were about 4% lower than the rate for individuals in the general population (48.2). (33) No articles summarized

Table 1

Baseline characteristics of patients enrolled in studies of treatment-resistant depression[a]

	Treatment-resistant depression								Treatment-responsive depression							
	N		%						N		%					
Characteristic	M	SD	M	SD	Median (%)	Minimum (%)	Maximum (%)	N of studies	M	SD	M	SD	Median (%)	Minimum (%)	Maximum (%)	N of studies
Sample size	1,239	4,756			42	6	24,415	49								
Age (M±SD)	46.7	5.3			47.0	27.4	74.7	39								
Age at onset (M±SD)	31.5	6.8			27.7	2.9	51.2	12								
Duration of illness (M±SD years)	4.4	3.3			16.7	2.5	26.7	20								
Previous episodes of depression (M±SD)	3.8	2.1			2.6	.8	7.2	16								
Women	14,310	6,086	71	4	65	0	93	42								
Race-ethnicity																
Caucasian	3,060	1,765	89	4	91	78	97	12								
African American	29	24	13	9	3	2	18	3								
Other	6	3	4	3	3	0	7	3								
Comorbid condition[b]																
Joint, limb, or back pain	3,386		73					1	5,267		70					1
Hypertension	3,095	607	67	0	40	12	68	2	5,035	903	67	9	43	17	68	2
Dyslipidemia	2,821	556	61	0	32	1	62	2	4,739	853	63	11	34	3	64	2
Cardiovascular disease	2,598		56					1	3,702	666	49	9	25	1	50	2
Malaise and fatigue	2,412		52					1	3,311		44					1
Anxiety	1,767	1,265	44	0	21	7	59	6	2,512	1,557	36	16	13	9	43	3
Anemia	3		39					1	2,633		35					1
Hypothyroidism	1,593	312	35	5	23	11	35	2	2,147	385	29	4	18	7	29	2
Chronic obstructive pulmonary disease	1,577		34					1	2,257		30					1
Diabetes	1,358	499	30	0	15	8	32	3	2,295	411	31	4	20	10	31	2
Alcohol abuse, lifetime	16	10	27	7	28	14	30	3	47		34					1
Alcohol abuse, current	231	173	6	2	5	3	8	3	180	116	3	1	2	1	3	2
Avoidant personality disorder	18	2	24	7	28	20	30	2	35		33					1
Asthma	974		21					1	1,354		18					1
Self-defeating personality disorder	11		21					1	15		14					1
Chronic pain	878	251	20	1	16	15	20	3	1,162	490	19	3	21	18	23	2
Substance use disorder, lifetime	8	4	18	12	14	7	39	3	30		22					1
Substance use disorder, current	56	42	3	1	43	1	4	2	37		2					1
Obsessive-compulsive disorder	13	2	17	4	18	15	21	2	39		37					1
Panic disorder	48	34	17	7	18	7	25	5	17		12					1
Delusions and other psychoses	774	151	17	2	13	9	17	2	444	80	6	1	4	2	6	2

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Table 1

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Characteristic	Treatment-resistant depression								Treatment-responsive depression							
	N		%					N of studies	N		%					N of studies
	M	SD	M	SD	Median (%)	Minimum (%)	Maximum (%)		M	SD	M	SD	Median (%)	Minimum (%)	Maximum (%)	
Obesity	774	152	17	3	10	3	17	2	1,037	185	14	1	104	6	14	2
Personality disorder	728	142	16	2	11	6	16	2	296	53	4	0	43	2	4	2
Sleep disorder	694	252	16	2	13	9	16	2	978		13					1

[a] SDs and minimum and maximum percentages are not reported when only one study provided results.

[b] The following list reports percentages of patients with treatment-resistant vs. treatment-responsive depression and other conditions: mixed personality disorder, 14% vs. data not reported (DNR); borderline personality disorder, 13% vs. 13%; paranoid personality disorder, 13% vs. 28%; migraine, 12% vs. 9%; social phobia, 12% vs. 35%; dependent personality disorder, 11% vs. 15%; simple phobia, 11% vs. 14%; generalized anxiety disorder, 10% vs. 16%; agoraphobia, 10% vs. 7%; passive-aggressive personality disorder, 9% vs. 13%; physical abuse, 9% vs. DNR; posttraumatic stress disorder, 9% vs. 4%; soft tissue disorder, 7% vs. 0%; somatoform disorder, 5% vs. 5%; antisocial personality disorder, 5% vs. 7%; eating disorder, 5% vs. 3%; narcissistic personality disorder, 4% vs. 10%; obsessive-compulsive disorder, 4% vs. 3%; acute myocardial infarction persistent, 3% vs. DNR; mood disorders, 3% vs. 1%; dysthymia, 3% vs. DNR; dementia, 2% vs. 2%; gastritis and duodenitis, 2% vs. 4%; schizoid personality disorder, 2% vs. 3%; phobic anxiety disorders, 2% vs. 3%; mild mental retardation, 1% vs. 2%; and histrionic personality disorder, 0% vs. 3%

associations between treatment-resistant depression and other outcomes, such as crime rates, incarceration, social services' utilization, or caregivers' quality of life.

Response and remission rates

Therapeutic options for treatment-resistant depression consisted of deep brain stimulation, transcranial magnetic stimulation, transcranial direct-current stimulation, vagus nerve stimulation, group psychoeducation, cognitive therapy, and a variety of drugs, most commonly lamotrigine, lithium, olanzapine, and venlafaxine. Sixteen studies reported rates of remission and response (Table 3) (8,9,17,38,43–54). Response rates for different treatment groups varied between 0% and 80%, for an average of 36%±1%. Remission rates varied from 8% to 80%, for an average of 20%±1%. The lowest average response and remission rates were reported in the STAR*D trial: scores on the QIDS–Self-Report–16 indicated that only 15% and 10%, respectively, had responded to treatment or were in remission (8). One study found cognitive therapy to be effective; patients averaged a significant 9-point decline in the Beck Depression Inventory score, and 26% had a "sustained recovery" at 26 weeks (55).

Medication-related adverse events

Twenty-seven studies reported on the incidence of adverse events among patients with treatment-resistant depression. Rush and others (56) found that 53% of patients experienced at least one adverse event, of which 81% were mild or moderate. The most frequent mild or moderate drug-related adverse events were decreased sexual desire (33%), orgasmic dysfunction (26%), and blurred vision (15%). The most frequent severe drug-related adverse events were dissociative reactions (13%), ataxia (13%), mixed states (dysphoric mania or agitated depression) (10%), and tremor and nausea (10%). The most frequent procedure-related adverse events were swollen eye (55%), headache (38%), and erythema (36%); no severe procedure-related adverse events were reported. Only four studies that reported adverse events had a placebo arm. Adverse events

Table 2

Baseline measures of symptom severity among patients with treatment-resistant depression[a]

Variable	M	SD	Median	Lowest	Highest	N of studies	Scale range		
							Remission or mild	Severe or markedly ill	Reference
Failed drug trials[b]	4.7	2.7	2.6	1.0	10.0	11			
Failed drug classes[b]	2.1	.3	2	2.0	3.0	6			
Depression-specific scale score									
HAM-D-17	21.9	1.7	22.6	19.2	28.4	18	0–13	20–52	22
HAM-D-21	19.8	5.2	19.5	15.8	23.2	2	0–15	23–64	22
HAM-D-24	27.9	4.2	27.9	21.0	33.7	4	0–18	27–75	22
HAM-D-28	30.4	5.5	32.2	23.7	34.3	3	0–10	21–52	23
MADRS	31.8	3.0	33.0	25.0	50.0	12	0–19	35–60	22
CGI-S	4.6	.4	4.8	3.8	6.3	11	1–3	6–7	24
BDI	30.9	6.6	31.7	16.5	38.2	5	0–18	30–63	22
IDS-SR-30	41.3	2.0	40.8	38.2	43.4	3	0–25	39–84	22
IDS-C-30	35.4					1	0–23	37–84	22
QIDS-SR-16	15.8	2.5	15.8	14.0	17.6	2	0–10	16–27	22
QIDS-C-16	14.4					1	0–10	16–27	22
Other scale score									
GAF	50.0	7.0	42.3	28.7	55.0	6	100–61	50–0	25
HAMA	17.8	1.1	19.6	17.5	23.3	4	0–17	31–56	26
Q-LES-Q	37.4	1.2	37.3	34.6	41.0	3	100	0	26
BPRS	17.3	6.9	25.9	16.0	35.8	2	16–31	53–126	27
SF–36 MCS	22.5	2.7	21.6	19.4	23.7	2	100	0	28
SF–36 PCS	37.5	3.1	36.5	34.0	38.9	2	100	0	28
BAI	14.1					1	0–15	26–63	29
MMSE	27.7					1	24–30	0–23	30
SQ-SS	6.6					1	0	18	31
SQ-SWB	1.4					1	6	0	31
POMS	52.5					1	0	200	32

[a] SDs and minimum and maximum scores are not reported when only one study provided results. HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Scale; CGI-S, Clinical Global Impression–Severity; BDI, Beck Depression Inventory; IDS, Inventory of Depressive Symptomatology; SR, Self-Report; C, Clinician Rated; QIDS, Quick Inventory of Depressive Symptomatology; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; BAI, Beck Anxiety Inventory; HAMA, Hamilton Anxiety Scale; MMSE, Mini-Mental State Examination; SF-36, Short-Form Health Survey Questionnaire; MCS, mental composite score; PCS, physical composite score; SQ, Symptom Questionnaire; SS, somatic subscale; SWB, somatic well-being; POMS, Profile of Mood States.

[b] Excluded studies that reported the number of failed drug trials and classes as ranges.

that occurred in more than 5% of the placebo groups were blood pressure change (40%), headache (15%), dissociative reaction (in a study utilizing ketamine) (13%), and manic reaction (13%) (10,48,54,57).

Quality of life and costs

Quality-of-life data were taken from published models that used data sources ranging from reviews of prior literature to original trials (58–63). The studies measured quality of life with a continuous scale, with 0 indicating death and 1 indicating perfect health. Average baseline scores were .552±.120 for patients with major depressive disorder (58–61), .826±.065 for patients in remission (59–63), .673±.031 for patients who responded to therapy without remission (61,62), and .417±.126 for patients who did not respond to therapy (61–63). Adverse events caused a further loss of .01 to .12 quality-of-life units (59).

Five studies provided detailed information about annual per-patient costs for treatment-resistant depression, one from Medicare and four from databases of national employers and private payer claims (Table 4) (33,36,54,64,65). Annual claims for visits to a medical facility were relatively common among patients with treatment-resistant (N=28.3 claims) versus treatment-responsive depression (N=15.1 claims) (64). Fifty-two percent of patients with treatment-resistant depression were hospitalized over their lifetimes (39).

Among private payers, the mean annual direct health care costs per patient for management of treatment-resistant depression ($13,196) were $5,481 higher than for management of treatment-responsive depression ($7,715) (Table 4) (36,64,65). These comparisons were from the same studies, so observed differences were not an artifact of sample heterogeneity. Annual direct medical costs for persons in the general population were $3,997 (64). Total costs in productivity per patient-year were $4,048 higher among patients with treatment-resistant depression ($6,924) than among patients with treatment-responsive depression ($2,876) (36,64) (Table 4). For the general population, annual productivity costs were $1,098 (64). The total annual direct and indirect costs per patient-year were $20,120 for patients with treatment-resistant depression and $10,592 for an age-matched population with treatment-responsive depression (Table 4)

Table 3

Rates of response and remission among patients with treatment-resistant depression, by study[a]

Study	Rating scale[b]	Length of study (weeks)	N of patients	Treatment with lowest rate of response or remission	Treatment with highest rate of response or remission	Response (%)			Remission (%)		
						Average	Lowest	Highest	Average	Lowest	Highest
Inoue et al., 1996 (50)	HAM-D-17	6	6	Bromocriptine		67					
Shelton et al., 2001 (51)	MADRS	8	34	Olanzapine	Olanzapine and fluoxetine	25	0	60			
Papakostas et al., 2003 (35)	HAM-D-17	6	92	Nortriptyline; patients with comorbid avoidant personality disorder	Nortriptyline; patients without comorbid avoidant personality disorder	42	17	49			
Seidman et al., 2005 (49)	HAM-D-17	6	23	Placebo	Testosterone	—	23	54			
Corya et al., 2006 (52)	MADRS	7	483	Olanzapine	Venlafaxine (response); olanzapine and fluoxetine combination (remission)	38	25	50	23	14	30
Fava et al., 2006 (8)	QIDS-SR-16	14	235	Mirtazapine	Nortriptyline	15	13	17	10	8	12
Fava et al., 2006 (8)	HAM-D-17	14	235	Mirtazapine	Nortriptyline				16	12	20
Doree et al., 2007 (46)	HAM-D-17	8	20	Lithium	Quetiapine	65	50	80	60	40	80
Doree et al., 2007 (46)	MADRS	8	20	Lithium	Quetiapine	65	50	80	55	30	80
Mahmoud et al., 2007 (48)	HAM-D-17	6	258	Placebo	Risperidone	—	30	46	25	11	25
Schindler and Anghelescu, 2007 (45)	HAM-D-17	8	34	Lithium	Lamotrigine	47	41	53	21	18	23
Avery et al., 2008 (17)	MADRS	9	158	Sham, then transcranial magnetic stimulation (TMS)	Extended TMS	40	34	45	25	18	31
Avery et al., 2008 (17)	MADRS	6	158	Sham, then TMS	Extended TMS	35	26	42	16	11	20
Avery et al., 2008 (17)	HAM-D-24	6	158	Sham, then TMS	Extended TMS	37	32	42	22	16	27
Avery et al., 2008 (17)	HAM-D-24	9	158	Sham, then TMS	Extended TMS	39	32	46	29	19	37
Bares et al., 2008 (9)	MADRS	4	25	Venlafaxine		48					
Karp et al., 2008 (47)	HAM-D-17	6.9	20	Duloxetine		50					
Lozano et al., 2008 (53)	HAM-D-17	26	20	Deep brain stimulation		60					
Lozano et al., 2008 (53)	HAM-D-17	52	20	Deep brain stimulation		55			35		
Bewernick et al., 2010 (23)	HAM-D-28	52	11	Deep brain stimulation		46			9		
Kopell et al., 2011 (44)	HAM-D-28	91	11	Epidural cortical stimulation		46			36		
Taneja et al., 2012 (54)	MADRS	6	1,034	Meta-analysis: antidepressant		30	20	39			
Taneja et al., 2012 (54)	MADRS	6	540	Meta-analysis: aripiprazole with antidepressant		49	41	60			
Taneja et al., 2012 (54)	MADRS	6	309	Meta-analysis: quetiapine 150 mg with antidepressant		34	28	40			
Taneja et al., 2012 (54)	MADRS	6	312	Meta-analysis: quetiapine 300 mg with antidepressant		38	32	44			
Taneja et al., 2012 (54)	MADRS	6	200	Meta-analysis: olanzapine and fluoxetine		45	32	64			
Average±SD (weighted)[c]		6±20	176±234			36±1	26±1	45±1	20±1	13±1	25±1

[a] For studies that assessed only one treatment, the treatment is listed under lowest response or remission rate, and results are listed under average response or remission rates.

[b] HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report

[c] Weighted by inverse-variance method. Excludes patients on placebo

(36,64,65). These costs were $5,095 in the general population (64).

Annual direct medical costs among Medicare patients were $20,736 for patients with treatment-resistant depression, $14,098 for patients with treatment-responsive depression, and $10,380 in the general population of Medicare patients (33). These differences in cost in the Medicare population reinforce the considerable health care benefit that could be obtained from more effectively treating major depressive disorder.

Discussion

Our review of literature shows that among the many burdens of patients with treatment-resistant depression, they experience only a 20% probability of achieving remission in the course of treatment, a 17% prevalence of prior suicide attempts, substantially lower quality-of-life scores than patients whose depression remits, and direct and indirect annual costs among private payers that are $9,529 higher than those of patients with treatment-responsive depression. Patients with treatment-resistant depression had 28.3 annual general medical visits, more than three times as many as the general population average of 8.7, whereas patients with treatment-responsive depression had less than twice as many annual general medical visits as the general population (64).

Although response and remission rates for patients with treatment-resistant depression varied widely among studies, average improvements on the CGI-S (36%), the HAM-D-17 (42%), and the MADRS (27%) were similar. The STAR*D study found particularly low rates of response (15%) and remission (10%), possibly because this study consisted of patients who did not respond to up to three well-monitored treatments, whereas many other studies used nonresponse to just one or two naturalistic treatments as their criterion for treatment resistance.

Among adults in the United States, the 12-month prevalence of major depressive disorder in 2012 was 6.7% (3), or 16 million individuals. Assuming that 12% of these patients had treatment-resistant depression, which was the lowest estimate reported by studies in this review (64), a total of 1.9 million adults in the United States had treatment-resistant depression in 2012. If annual costs of treatment per patient-year for private payers totaled $20,120, as estimated, the total costs for treatment of this population in 2012 was $38 billion. Adding in the annual cost of treatment of the 14 million patients with treatment-responsive depression ($10,592 each; $148 billion total), the societal burden of major depressive disorder for the United States in 2012 was $188 billion. By comparison, the societal cost for cancer was $131 billion (66), and in 2007, the societal cost for diabetes in 2012 dollars was $173 billion (67).

Corey-Lisle and colleagues (64) stated that treatment resistance among patients with depression might actually be as high as 20%. When this higher estimate was used, the estimated societal burden of major depressive disorder in the United States reaches $200 billion per year and the burden of treatment-resistant depression alone reaches $64 billion per year. A prior study estimated that the societal cost of major depressive disorder was $124 billion per year, in 2012 dollars (2). This estimate may be lower than our estimate of $188–$200 billion because of temporal changes in unit service costs, for example, increasing wages, and the possible exclusion of costs for patient visits that were not reported as being primarily for depression (36,64).

The burden of major depression can also be calculated as an increase in costs above those of the general population. If 12% of patients with depression are resistant to therapy, the costs of depression above general population costs are $29 billion for patients with treatment-resistant depression, $77 billion for patients with treatment-responsive depression, and $106 billion for all major depression. If 20% of depressed patients are resistant to therapy, the estimated costs are $48 billion for patients with treatment-resistant depression, $70 billion for patients with treatment-responsive depression, and $118 billion for all major depression. Conversely, if 70% more patients respond to antidepressant therapy, the costs for the 3.6% of patients who remain treatment resistant would decrease to $8.6 billion, and costs for patients with treatment-responsive depression would be $84.3 billion. The aggregate $93 billion annual cost of major depression above general population costs would save $13 billion, a 12% reduction in the annual cost of treating all patients with major depressive disorder.

Gillum and colleagues (68) recently compared 29 common conditions and diseases in terms of incidence, prevalence, and disability-adjusted life years. Depression ranked first in populationwide burden by disability-adjusted life years. The next four most impactful conditions or disorders were injuries, ischemic heart disease, alcohol abuse, and chronic obstructive pulmonary disorder. The low quality-of-life scores (.417 on a scale of 0 to 1) reported by patients with treatment-resistant depression who did not respond to therapy fell within the range of scores reported for metastatic cancer, chronic moderate-to-severe pain, or acquired blindness (20). Although these quality-of-life measures may be confounded by patients' current mood and depressive symptoms (69), the estimates amount to one million quality-adjusted years lost due to treatment-resistant depression in the United States. Treatment-responsive depression accounts for an additional loss of more than 1.5 million quality-adjusted years.

The small numbers and heterogeneity that characterized the study populations and treatments described in the articles summarized here may limit the general applicability of some findings. For example, only a few studies included information about comorbid disorders and adverse events. Our summaries of the five studies that reported costs per patient-year for depression treatment and our extrapolation of the data to determine nationwide costs can be combined with results of future studies to more accurately calculate the monetary impact of treatment-resistant depression. Other limitations of this analysis included the heterogeneity of methods and the degree to which complete findings were reported, the relatively

Table 4

Costs per patient-year for patients with treatment-resistant and treatment-responsive depression, by resource category[a]

Category	M	SD[b]	Median	Lowest	Highest	N of studies
Treatment-resistant depression						
Health care (direct costs)						
Depression drugs	2,667	1,026	3,736	1,346	7,568	4
Nondepression drugs	2,556	141	2,580	2,216	2,963	3
Hospitalizations						
Emergency care	392	—	—	—	—	1
Nonpsychiatric medical care	2,508	786	2,986	2,253	3,719	2
Psychiatric visits	593	324	790	488	1,092	2
Physician visits	4,829	2,431	3,351	1,085	5,618	2
Psychotherapy	978	344	770	449	1,090	2
Total[c]	13,196	219	13,402	13,152	14,417	3
Productivity (indirect costs)						
Absenteeism	2,625	987	2,025	1,105	2,945	2
Disability	4,299	815	3,804	3,044	4,564	2
Total	6,924	1,801	5,829	4,149	7,509	2
Total direct and indirect costs	20,120					
Treatment-responsive depression						
Health care (direct costs)						
Depression drugs	898	162	561	385	939	3
Nondepression drugs	1,407	75	1,369	1,094	1,422	3
Hospitalizations						
Emergency care	224	—	—	—	—	1
Nonpsychiatric medical care	1,438	119	1,418	1,332	1,505	2
Psychiatric visits	99	23	95	79	112	2
Physician visits	1,708	1,864	2,021	666	3,376	2
Psychotherapy	255	176	284	156	412	2
Total[c]	7,715	456	6,902	6,375	7,832	3
Productivity (indirect costs)						
Absenteeism	1,125	849	1,268	651	1,885	2
Productivity	1,751	464	1,829	1,492	2,166	2
Total	2,876	1,312	3,096	2,142	4,050	2
Total direct and indirect costs	10,592					

[a] Costs are for private payers and are reported in 2012 dollars.
[b] An SD and other data were not reported when only one study provided results.
[c] May include other costs that are not listed

short periods of patient follow-up, and a focus primarily on clinical endpoints during follow-up.

The burden of treatment-resistant depression was likely underestimated because there is limited published research, or none at all, on the incidence of crime rates, incarceration, and use of social services among persons with depression and on costs and quality-of-life burden for family members and caregivers. The burden might also have been underestimated because we excluded studies with adolescent populations, which have similar prevalence rates for depression as adults but lower treatment rates (70–72). Among patients with treatment-resistant depression, adolescents experienced a greater burden with regard to suicide attempts compared with adults, and their rate of substance use disorders (54%) was higher than the current (3%) and lifetime (18%) rates for adults (73).

In response to these challenges, personalized medicine technologies are finding increasing application in reducing the burden of major depression. One such approach, pharmacogenomics, matches the pharmacokinetic and pharmacodynamic properties of antidepressant medications to the genetic profile of individual patients. Pharmacogenomic test results can identify variability in psychiatric drug response and, when applied clinically, can increase antidepressant responses by 70% (74–78). Identifying the right medication and dose for patients will shorten patients' treatment odyssey, thereby decreasing the proportion that become treatment resistant. The resulting savings would diminish annual health expenditures and increase productivity. Psychiatric pharmacogenomics and other innovations may also improve the classification of major depressive disorder subtypes; define more individualized and earlier, potentially prodromal treatments; and reduce adverse event rates (79,80).

Conclusions

The studies reviewed here reveal that the personal and societal burdens of depression are disproportionately greater among patients who do not respond to antidepressant therapies. Contributory factors to this extra burden include more unsuccessful drug trials; more comorbid disorders, such as malaise, fatigue, and anxiety; and increases in suicidal ideation. The far greater personal financial burden of treatment resistance is likely to compound anxiety, depression, and comorbid disorders as financial hardships mount.

Despite multiple treatment options available to clinicians, treatment resistance remains highly prevalent and exacts a substantial toll on patients' quality of life and on society. The burden of treatment-resistant depression is on a par with or is greater than that of other chronic conditions such as cancer and diabetes, yet depression ranks only 15th among conditions or disorders that receive National Institutes of Health research funds (68).

Improvements in technology are likely to diminish treatment resistance and mitigate its extra costs. These include pharmacogenomic tests that incorporate additional DNA variants and DNA methylation status; new medications that are based on nonmonoaminergic approaches, such as N-methyl-D-aspartate receptor antagonism; and refinements in transcranial magnetic stimulation.

Disparities in care also need to be addressed so that innovations can achieve a broad societal impact. Certain racial or ethnic groups and unemployment are associated with underdetection of mental illness and inadequate mental health care access or quality (81–84). Solutions include more social programs, better patient education, quality improvement programs, and

increased resources for indigent care clinics (81–84). Consistent processes for assessing regulatory and reimbursement implications of new therapeutic and diagnostic practices are also needed (79). Expanded treatment alternatives, augmented with pharmacogenomic decision support, have the potential to improve outcomes and help patients retain productive lives. Along with decreases in health care costs and increased global productivity, there is much to achieve—and expect—by decreasing the individual and societal burdens of treatment-resistant depression.

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Submissions Invited for Column on Integrated Care

The integration of primary care and behavioral health care is a growing research and policy focus. Many people with mental and substance use disorders die decades earlier than other Americans, mostly from preventable chronic medical illnesses. In addition, primary care settings are now the gateway to treatment for behavioral disorders, and primary care providers need to provide screening, treatment, and referral for patients with general medical and behavioral health needs.

To stimulate research and discussion in this critical area, *Psychiatric Services* has launched a column on integrated care. The column focuses on service delivery and policy issues encountered on the general medical–psychiatric interface. Submissions are welcomed on topics related to the identification and treatment of (a) common mental disorders in primary care settings in the public and private sectors and (b) general medical problems in public mental health settings. Reviews of policy issues related to the care of comorbid general medical and psychiatric conditions are also welcomed, as are descriptions of current integration efforts at the local, state, or federal level. Submissions that address care integration in settings outside the United States are also encouraged.

Benjamin G. Druss, M.D., M.P.H., is the editor of the Integrated Care column. Prospective authors should contact Dr. Druss to discuss possible submissions (bdruss@emory.edu). Column submissions, including a 100-word abstract and references, should be no more than 2,400 words.